The Dialogue Between Bones and Organs: Its Potential Clinical Relevance

There’s much more to bone than meets the eye. So believes Gerard Karsenty, MD, PhD, Professor and Chair of Genetics and Development, NewYork-Presbyterian/Columbia University Medical Center, who for two decades has studied every aspect of skeletal biology, ranging from cell differentiation to function. In the last 10 years, he and his Columbia colleagues have explored through genetic and molecular means the hypothesis that the control of bone mass and energy metabolism must be coordinated in large part by hormones like leptin and more recently osteocalcin that appear during evolution with bone.

At the core of Dr. Karsenty’s research is a belief that there are many new physiological pathways to be discovered in mammals. “Our aim is not so much to identify novel regulatory molecules involved in known functions, but rather to identify, study, and elucidate at the molecular level totally novel functions for various organs,” says Dr. Karsenty. “To test this hypothesis we use the skeleton as a model organ and the mouse as a model organism.”

Predicting Metabolic Consequences of HIV and Its Treatment

Patients with HIV under medical treatment can now, as a matter of course, grow older, no longer threatened by insidious infections and virulent cancers. They are reliably protected by precisely designed antiretroviral drug regimens developed through long-term research intended to inhibit the replication of the virus so that it remains below detectable and lethal levels. The use of these antiretroviral drugs, initially AZT in the late 1980s, has been halting the development of the severe infections resulting when a patient’s HIV transitioned into AIDS.

“Since the advent of these therapies, there were suggestions that HIV itself, as well as the therapies, could have other potential complications,” says José O. Alemán, MD, PhD, an endocrinologist with NewYork-Presbyterian/Weill Cornell Medical Center, and an instructor in clinical investigation, The Rockefeller University. “What became evident as these treated patients aged is that while they no longer die of opportunistic infections, they are now at risk for serious, chronic diseases, especially cardiovascular disease, and, to an alarming degree, a higher incidence of diabetes mellitus. That observation led a number of groups, including ours, to ask about the predisposition of patients with HIV who are treated with antiretroviral therapies to chronic diseases that affect the general population and how they are similar or different.”

During his medicine residency and endocrinology fellowship at NewYork-Presbyterian/Weill Cornell, Dr. Alemán began studying these questions under the mentorship of Marshall Glesby, MD, PhD, an infectious disease specialist with a particular
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“One implication of this hypothesis is that bone should lack an organ that would regulate reproduction and energy metabolism. It is not the only implication, but it is a major one. This hypothesis implies that there is a dialogue, a two-way street between bone and organ regulating energy metabolism or reproduction. And this has to be done through blood or nerves.”

In the context of this hypothesis, Dr. Karsenty tested whether the bone-specific secreted molecule osteocalcin regulates glucose metabolism. “We have shown that this hormone acts on the pancreas to increase insulin secretion and sensitivity,” says Dr. Karsenty.

In his lab studies, mice that were engineered to lack osteocalcin became glucose intolerant, but when provided osteocalcin, their insulin sensitivity and blood sugar returned to normal. “As a result, we determined that osteocalcin is needed in mice that are fed a normal diet to maintain glucose homeostasis,” he says.

Dr. Karsenty has also shown that bones play an important role in fertility. In 2011 in an article published in Cell, he demonstrated that mice that did not produce osteocalcin had abnormally low levels of testosterone and were sterile. However, mice that produced high levels had more testosterone and bred frequently.

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— Dr. Gerard Karsenty

“So all these functions suggest that osteocalcin is necessary to maintain glucose homeostasis and male fertility in mice and we now have evidence in humans,” he says. “We have tested this by injecting osteocalcin in mice fed a high fat diet and in mice that were sterile, and in both cases we have been able to show that we improved glucose homeostasis, and we were able to improve testosterone production. The idea that this hormone may have a therapeutic relevance is at the heart of our work.”

In recent investigations into the biology of osteocalcin, Dr. Karsenty has demonstrated that it is needed for the development of the hippocampus and for cognitive functions. “The powerful regulation of bone mass exerted by the brain suggests the existence of bone-derived signals modulating this regulation or other functions of the brain,” says Dr. Karsenty. “We have established that osteocalcin crosses the blood-brain barrier, binds to neurons of the brainstem, midbrain, and hippocampus, and enhances the synthesis of all monoamine neurotransmitters. It also inhibits GABA synthesis, prevents anxiety and depression, and favors learning and memory independently of its metabolic functions.

The hope is that this hormone could have a therapeutic relevance, probably more in age-related memory loss and decrease in cognition that comes with age rather than with a disease,” says Dr. Karsenty. “And the reason for that is that there is no other treatment for age-related decrease in cognition. There is no way to treat for that.”

Dr. Karsenty’s lab has also shown recently that gut-derived serotonin is a hormone whose main function is to inhibit bone formation by osteoblasts in mice and humans. Because they have elucidated the entire molecular cascade from the synthesis of the hormone to its target genes in osteoblasts, they are now in a position to test the therapeutic relevance of this pathway in the treatment of osteoporosis.

“This work on serotonin has triggered a more general interest in the lab about the possible role and mechanism of action of brain-derived serotonin in the control of bone mass,” says Dr. Karsenty. “These projects focused on serotonin regulation of bone mass and address both basic physiological functions and its potential therapeutic outcome in humans.”

Going forward, Dr. Karsenty’s research is geared to move in two directions. “The first is to demonstrate that osteocalcin is not only necessary, but sufficient, and therefore that it can have a therapeutic appeal,” he says. “And the second direction, which is equally important from a medical point of view, is to look for all the functions regulated by osteocalcin and identify other functions in other organs for which osteocalcin could have a therapeutic implication or relevance.

“I think bone affects or influences more diseases than simply osteoporosis,” he adds. “It affects the severity of many other diseases, dysfunction of glucose metabolism, decrease of cognition, decrease of fertility. And all of these diseases occur with age precisely when bone mass decreases.”

Reference Articles

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focus on clinical research related to complications of HIV disease and its treatment, and Kyu Y. Rhee, MD, PhD, Associate Professor of Medicine and Associate Professor of Microbiology and Immunology, Weill Cornell Medical College. Dr. Alemán and his collaborators focused on studying metabolic complications from either the lingering presence of the virus or as a consequence of the antiretroviral drugs and, more specifically, how closely metabolically do HIV patients resemble patients who are not infected with the virus for developing type 2 diabetes mellitus. Their goal was to identify metabolic markers that would indicate the onset of diabetes before symptoms are manifested.

Tapping Into the Women’s Interagency HIV Study

“Dr. Glesby had been instrumental in organizing a collaborative project with the Women’s Interagency HIV Study, an ongoing NIH multicenter study of urban women who are either HIV infected or at risk for HIV acquisition,” says Dr. Alemán. “The study researchers developed a large database on the order of thousands of patients and had looked at some of the complications from HIV infections or the antiretroviral treatment, including cardiovascular disease, and more specific to the work that we do in my subgroup, diabetes. Because the patients were being followed prospectively, we could look back at blood samples taken before they developed diabetes. By doing this, we were able to identify an initial plasma signal in these patients, which just by virtue of having HIV and being treated, put them at higher risk than the general population of developing diabetes.”

Simultaneously, a number of groups had published studies showing that an old phenomenon of changes in branched chain amino acid levels in blood could now be detected using mass spectrometry, enabling the identification of patients at risk for developing diabetes.

“The ability of measuring these amino acids, in parallel, in the form of mass spectrometry, allowed us to create a signature of essential amino acids,” explains Dr. Alemán. “In addition to standard clinical measurements, such as body mass index and fasting glucose, this signature was found to be predictive of the development of diabetes. With these two pieces of information, we thought to ask in the Women’s Interagency HIV Study if we would be able to observe any changes in the plasma metabolites, as well as explicit amino acid changes, in the women known to be at risk of developing diabetes. The short answer was that we could.”

In 2013, Dr. Alemán – a fellow at the time – and his colleagues presented their findings related to the detection of that signature at a fellowship research award ceremony. “A subset of 51 women out of the 153 women in our patient pool had blood samples at the time of their diabetes diagnosis,” says Dr. Alemán. “We had at least one, if not multiple, blood samples preceding the diagnosis, so we were able to make the prediction moving forward. We found an essential amino acid signature that is actually very similar to what was found by other investigators. This helped to clarify whether or not the diabetes that develops in HIV-infected women is similar to that of the general population or is there something in particular to them having the HIV or being treated for the HIV. In our study, the amino acid signature that we detected suggested that the metabolic changes preceding diabetes are similar to that of the general population.”

Dr. Alemán and his research team are now building on their initial observation with a study in another two groups of 51 HIV-infected women to not only validate this signature, but also to try to detect new metabolite changes that might be distinguished from the general population and correlate this metabolic signature in plasma to all of the other clinical parameters that are used to predict the risk of diabetes. “In other words,” says Dr. Alemán, “after finding a plasma signature of essential amino acid elevation in HIV-infected women that closely relates to what is found in the general population, we are now trying to place this information in the context of clinical values that physicians may obtain on patients. We went into the study thinking that diabetes development would be more aggressive and, perhaps, unrelated to the general population. At this point, the signature tells us that is not the case.”

Counting the advances made in using mass spectrometry to look at patterns of plasma metabolites, Dr. Alemán notes, “We now have the ability to measure these metabolites in patient populations. We can use that as a way to predict the development of diabetes in the general population or in special populations, such as HIV-infected women. Its clinical use is still being developed.”

While this current analysis did not yet illuminate the mysteries of the unique processes of what makes HIV-infected patients at risk for diabetes mellitus, the efficacy and power of these markers in detecting a predisposition to type 2 diabetes makes the measuring of plasma metabolites a potentially powerful clinical tool.

Reference Articles

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